Original Article

The effects of integrated palliative care on quality of life and psychological distress in patients with advanced cancer: a systematic review and meta-analysis

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Background: Integrated palliative care (IPC) is regarded as the standard therapy for advanced cancer. We conduct a comprehensive analysis to evaluate current evidence for the effectiveness of IPC on quality of life (QoL) and psychological distress among patients with advanced cancer. Differences in effectiveness are explored regarding various types of IPC and the follow-up time/period.

Methods: A systematic literature search of PubMed, PsycINFO, EMBASE, CINAHL, and Cochrane Central Register of Controlled Trials was conducted. We identified 12 randomized controlled trials, which included 2,356 participants, that were pooled using a random-effects meta-analysis.

Results: Our results suggested no significant difference between the three different models of IPC and conventional treatment on overall QoL (SMD =0.06, 95% CI: –0.06 to 0.17, P=0.318). However, there was a long-lasting favorable effect of IPC on overall QoL throughout the follow-up period of 12 to 18 weeks (SMD =0.13, 95% CI: 0.02 to 0.24, P=0.016). The inpatient consulting model was more effective than other models in reducing depression and anxiety symptoms (SMD =–0.42, 95% CI: –0.64 to –0.19, P<0.001; SMD =–0.31, 95% CI: –0.54 to –0.09, P=0.006). In the early period of approximately 2 weeks of follow-up, IPC was shown to be significantly more effective in reducing depression and anxiety symptoms (SMD =–0.30, 95% CI: –0.52 to –0.07, P=0.009; SMD =–0.45, 95% CI: –0.68 to –0.23, P<0.001). IPC was also effective in decreasing posttraumatic stress disorder (PTSD) symptoms (SMD =–0.46, 95% CI: –0.69 to –0.23, P<0.001).

Conclusions: IPC can effectively improve QoL and alleviate early psychological distress in patients with advanced cancer. The inpatient consulting model of IPC was more effective than other models in reducing depression and anxiety symptoms.

Keywords: Palliative care; advanced cancer; quality of life (QoL); psychological distress; meta-analysis

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Introduction

Cancer rates are increasing globally, particularly in developing countries. According to the latest World Health Organization data, the global cancer burden reached 19.3 million new cases in 2020, with one in 5 people worldwide developing cancer during their lifetime, and one in 8 men and one in 11 women dying from the disease (1). As clinical symptoms are not always obvious in the early stages, most patients with malignancy are diagnosed in the late stage (2). In advanced cancer, survival is commonly <1 year (3), and the distressing symptoms most commonly reported by people include fatigue, breathlessness, pain, and anorexia (4). These symptoms usually become gradually aggravated with the tumor progression, which may result in major psychological distress and worse health-related quality of life (QoL).

Integrated palliative care (IPC) is a multidisciplinary approach that mainly aims to evaluate and treat physical, functional, psychological, social, and spiritual symptoms to improve QoL and general psychological distress of both patients and families (5,6). Currently, IPC is regarded as the standard therapy for chronic and progressive diseases, especially advanced and terminal cancer (7). Several studies have been conducted in recent years to assess the effects of IPC on mental health and QoL among terminally ill cancer patients, but the outcomes of these studies have varied. One meta-analysis focused only on integrated outpatient palliative care for patients with advanced cancer (8). Another recent meta-analysis, published in 2021, was performed on studies of multidisciplinary palliative care in advanced disease (9).

These two meta-analyses on IPC have strictly treated randomized controlled trials (RCTs) as an inclusion criterion. Fulton *et al.* (8). reviewed integrated outpatient palliative care for advanced cancer patients and found that short-term QoL improved (10 studies; SMD =0.24; 95% CI: 0.13 to 0.35) and symptom burden improved (five studies; SMD =−0.25; 95% CI: −0.39 to −0.11); however, there was no short-term effect on depressive symptom severity reporting as a continuous outcome (two studies; SMD =−0.09; 95% CI: −0.32 to 0.1). Oluyase *et al.* (9) reviewed hospital-based specialist palliative care for advanced illness and found improvement in patients' health-related QoL (10 studies; SMD =0.26; 95% CI: 0.15 to 0.37) and patient satisfaction with care (two studies; SMD =0.36; 95% CI: 0.14 to 0.57), as well as a significant reduction in patient symptom burden (six studies, SMD =−0.26; 95% CI: −0.41 to −0.12) and patient depression (eight studies; SMD =−0.22; 95% CI: −0.34 to −0.10).

Although a previous meta-analysis also showed that IPC could reduce psychological distress and improve QoL (9,10), few meta-analyses have taken into account that the various integration models may have different effects in patients with advanced cancer. In addition, no previous meta-analysis on IPC's long-term efficacy has been conducted. Therefore, characteristics of the time course of the efficacy of IPC on cancer-related outcomes need to be identified. To facilitate evidence-based health care, the outcomes of multiple studies must be aggregated. Thus, the purpose of this meta-analysis was to synthesize evidence from published studies to assess the effects of IPC on psychological distress and QoL among patients with advanced cancer. We present the following article in accordance with the PRISMA reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-162/rc).

Methods

Search strategy

A systematic literature search of PubMed, PsycINFO, EMBASE, CINAHL, and Cochrane Central Register of Controlled Trials was conducted from inception to August 15, 2019, and the search was updated on September 07, 2021. The search string included a combination of synonyms for neoplasms, palliative care, psychological distress, QoL, and randomized controlled trials (Appendix 1). The reference lists of the retrieved literature were further searched to identify any relevant gray literature. Two reviewers completed the screening process independently, and disagreement were resolved by the third reviewer.

Eligibility criteria

Inclusion criteria

The current meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist (11). We included randomized controlled trials reporting on the effectiveness of IPC interventions provided to adult patients (≥18 years) with terminal or advanced cancer. Interventions could be conducted in any setting, including primary care settings, hospitals and community settings. Studies were included if they assessed the outcomes of psychological distress or QoL. Specific outcomes for searching the relevant literature were not limited.

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Exclusion criteria

Non-randomized comparative studies and before-and-after studies were excluded. Studies that included newly diagnosed cancer patients, usually at stages I or II, were excluded. Studies that included a substantial proportion of patients with nonmalignant cancer and other illnesses were also excluded due to disparities in trajectories of decline leading to death and in patients' physical and mental conditions (12). Given the focus of this meta-analysis on IPC in particular, rather than on spiritual interventions or psychotherapies in general, we excluded studies that applied dignity therapy and studies that connected the patients to nature or to the sacred, as well as studies of psychosocial intervention.

Literature quality evaluation

We used the Cochrane risk of bias assessment tool (13) to assess the RCTs' methodological quality, risk of bias in selection, performance, detection, attrition, reporting, and other factors. Two independent reviewers independently appraised risk of bias and then provided a summary assessment for each study. No study was excluded as a result of findings from the risk of bias assessment.

Statistical method

Statistical analyses were performed with STATA version 15.0 software. Standardized mean differences (SMDs) were calculated for the pooled effects. All estimations are presented with their 95% confidence intervals (95% CIs). All pooled outcome measures were determined using random-effects models. The magnitude of heterogeneity among the included studies was assessed using the chi-squared test (Chi^2) and I-squared statistic (I^2). For the Chi^2 test, a Cochran's Q P value of <0.10 was considered significant. An I^2 value of more than 75% was considered to indicate a high degree of heterogeneity, 50–75% was moderate, and 25–50% was a low degree of heterogeneity (14). Sensitivity was examined by assessing the effect of a single study on the overall pooled estimates. Publication bias was evaluated using Egger's test, and P>0.05 represented the absence of publication bias.

Results

Study selection

Our literature database search yielded 3,644 records, and an additional search yielded 17 more records. After removing duplicates, 2,880 records remained. Of those, 2,791 records were excluded after screening titles and abstracts. Full reports of 89 publications were acquired, and 61 publications were further excluded for various reasons (*Figure 1*). As a result of the eligibility check, 12 articles were finally included. For a further description of our screening process, see the PRISMA study flow diagram (*Figure 1*).

Study characteristics

The studies were all from 5 high-income countries (United States, Denmark, Italy, Switzerland and Belgium). Ten trials (15-24) included patients with various cancers, and two trials (25,26) only included leukemia patients. Several outcomes that had been measured most frequently (i.e., overall QoL and psychological distress) were selected for our meta-analysis. Psychological distress includes depression, anxiety, and posttraumatic stress disorder (PTSD) symptoms. All included studies involved IPC as the primary intervention. We divided interventions into three models: the inpatient consulting model; the hospital outpatient model; and the model involving multiple settings. The follow-up assessments started anywhere from the completion of the intervention to half a year later (*Table 1*).

Risk of bias assessment

In all studies, there was a low or unclear risk of bias for most items (Figure S1), except for the presence of performance bias due to the lack of a double-blind design in seven studies. All trials were described as randomized, while 2 of the 12 (17%) did not describe the method used and were assessed as having an unclear risk. Allocation concealment was assessed as high risk in one trial (8%) and unclear risk in three trials (25%). Five trials (25%) were judged to have a high risk of attrition bias because more than 20% of participants dropped out. Attrition was caused by severe illness, exhaustion/weakness, hospital admission, transfer of care, death, failure to complete questionnaires and lack of interest. Nine trials (75%) had a protocol and were judged as having a low risk of selective reporting. Three trials (25%) were judged as having an unclear risk since the study protocols were not available and we did not have enough information in the study report to assess selective reporting.

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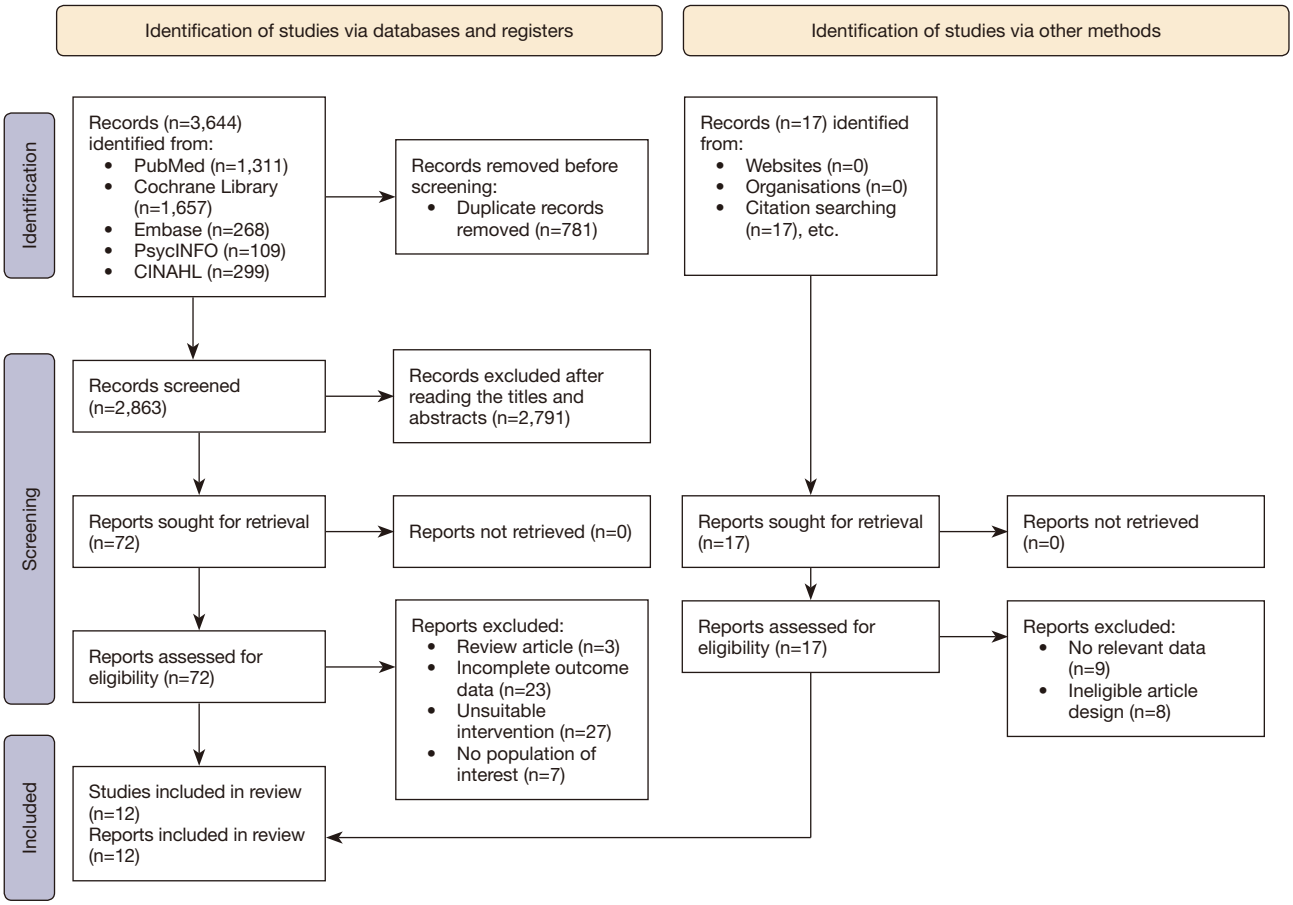

Figure 1 PRISMA flow chart of study selection.

QoL and psychological distress outcome measures

QoL was evaluated with different measures, including the European Organization for Research and Treatment of Cancer Quality of Life-C30 questionnaire (EORTC QLQ-C30) (27), and the Functional Assessment of Cancer Therapy-General (FACT-G) (28). Psychological distress was assessed with the Hospital Anxiety and Depression Scale (HADS) (29), Patient Health Questionnaire 9 (PHQ-9) (30), and PTSD Checklist–Civilian version (PCL-C) (31).

Effects on overall QoL

We determined the pooled effect size of IPC on QoL and compared it to the QoL of the control group in a random effects model. The overall effect size showed no significant difference between the two groups' QoL scores (SMD =0.06; 95% CI: –0.06 to 0.17; P=0.318) (*Figure 2*). Pooled data were homogeneous (I^2=34.6%, P=0.131). Furthermore, subgroup analyses were conducted to explore the impacts of different intervention models. In the subgroup analyses, a statistically significant difference was not found for the three different models versus conventional treatment (SMD multiple =0.11, P=0.204; SMD outpatient =–0.04, P=0.717; SMD inpatient =–0.09, P=0.611) (*Figure 2*). Sensitivity analysis was carried out by sequentially omitting each study. There was no alteration in the results, which indicated that our results were statistically reliable and robust. The sensitivity analysis is detailed in Figure S2. We further calculated whether the QoL score of the IPC group change differed at each time period in comparison to the conventional treatment group. At the 3–4 weeks and 6–8 weeks follow-ups, no significant difference in QoL was found between the groups (SMD =–0.08, 95% CI: –0.21 to 0.06, P=0.264; SMD =–0.06, 95% CI: –0.22 to 0.11, P=0.499). At the 12–18 weeks follow-up, there was a significant effect; there was a greater improvement in QoL

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Table 1 Study characteristics

Reference	Country	Sample type	N (each group)	Age (years, mean)	Design type	Duration	Control group type	Assess period	Outcome measure
Clark *et al.*, 2012	America	Advanced cancer (0–50% expected 5-year survival rate) diagnosed within 12 months	65, 66	58.7, 59.9	Hospital outpatient model: structured multidisciplinary intervention	The six 90-minute sessions	Standard oncologic care	Baseline, 4 weeks, 27 weeks	FACT-G
McCorkle *et al.*, 2015	America	Advanced cancer diagnosed within 100 days	66, 80	60	Hospital outpatient model: multidisciplinary outpatient consultation team	10 weeks	Usual care	Baseline, 1 month, 3 months	SDS, PHQ-9, ESDS, SF-12, FACT-G, HADS, MUIS-Community Form, SEMCD-6
El-Jawahri *et al.*, 2016	America	Haematologic malignancies undergoing autologous/ allogeneic HCT	81, 79	57.2, 56.9	Inpatient consulting model: integrated early palliative care	Period of hospitalisation	Standard transplant care	Baseline, 2 weeks, 3 months	FACT-BMT and Fatigue subscale, HADS, PHQ-9, ESAS, PCL-C
Grudzen *et al.*, 2016	America	Emergency Department patients with advanced cancer	69, 67	55.1, 57.8	Inpatient consulting model: IPC	Enrolment to discharge from hospital	Usual care	Baseline, 6 weeks, 12 weeks	ECOG, FACT-G, PHQ-9
Groenvold *et al.*, 2017	Denmark	Advanced cancer	145, 152	69.5	Model involving multiple settings: integrated early palliative care	8 weeks	Standard oncologic care	Baseline, 3 weeks, 8 weeks	EORTC QLQ-C30
Temel *et al.*, 2017	America	Incurable lung or non-colorectal GI cancer diagnosed within 8 weeks	175, 175	65.6, 64	Model involving multiple settings: integrated early palliative care	At least once per month until death	Standard oncologic care	Baseline, 12 weeks, 24 weeks, 2, 4, 6 months before death	FACT-G, PHQ-9, HADS
Vanbutsele *et al.*, 2018	Belgium	Advanced cancer, life expectancy of 12 months	92, 94	64.5, 65	Model involving multiple settings: integrated early palliative care	At least once per month until death	Standard oncologic care	Baseline, 12 weeks, 18 weeks, 24 weeks	EORTC QLQ-C30, MQOL, PHQ-9, HADS
Franciosi *et al.*, 2019	Italy	NSCLC, pancreatic, gastric or biliary tract cancer diagnosed within the previous 8 weeks, life expectancy greater than 3 months	142, 139	68.5, 68	Model involving multiple settings: integrated early palliative care	6 months	Standard oncologic care	Baseline, 12 weeks	FACT-G, ECOG

Table 1 *(continued)*

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Table 1 *(continued)*

Reference	Country	Sample type	N (each group)	Age (years, mean)	Design type	Duration	Control group type	Assess period	Outcome measure
Johnsen *et al.*, 2019	Denmark	Stage IV cancer according to the TNM classification or cancer in the central nervous system grade 3 or 4	145, 152	–	Model involving multiple settings: integrated early palliative care	8 weeks	Standard oncologic care	Baseline, 3 weeks, 8 weeks	EORTC QLQ-C30, HADS, FAMCARE-P16
Nipp *et al.*, 2020	America	Incurable gastrointestinal or lung cancer diagnosed within 8 weeks, aged >64 years	30, 32	73.9, 73.7	Hospital outpatient model: integrated early palliative care	2 in-person visits	Usual care	Baseline, 12 weeks	FACT-G, ESAS-r, GDS, ADLs, IADLs
El-Jawahri *et al.*, 2021	America	High-risk AML, received intensive chemotherapy	86, 74	64.4, 64.4	Inpatient consulting model: integrated early palliative care	At least twice per week during their initial and subsequent hospitalizations	Usual care	Baseline, 2 weeks, 4 weeks, 12 weeks, 24 weeks	FACT-Leukemia, HADS, PHQ-9, ESAS, PCL-C
Eychmüller *et al.*, 2021	Switzerland	Non-small cell lung, colorectal, castration-refractory prostate, breast cancer with visceral metastases, bladder and pancreatic cancer diagnosed within 16 weeks, not amenable or not responsive to curative treatment	74, 76	67.3, 67.3	Hospital outpatient model: integrated early palliative care	A 50 min structured conversation within 16 weeks of enrollment	Usual care	Baseline, 2 months, 4 months, 6 months	FACT-G, LSNS-6, DT

Intervention strategies: structured multidisciplinary intervention: addressed the five domains of QoL including cognitive, physical, emotional, spiritual, and social functioning. FACT-G, Functional Assessment of Cancer Therapy-General; SDS, Symptoms Distress Scale; PHQ-9, Patient Health Questionnaire 9; ESDS, Enforced Social Dependency Scale; SF-12, 12-Item Short Form Survey; HADS, Hospital Anxiety and Depression Scale; MUIS, Mishel Uncertainty in Illness Scale; SEMCD-6, Self-Efficacy for Managing Chronic Disease Scale; FACT-BMT, FACT-Bone Marrow Transplant; ESAS, Edmonton Symptom Assessment System; PCL-C, Posttraumatic Stress Disorder Checklist Civilian Version; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life-C30 questionnaire; MQOL, McGill Quality of Life Questionnaire; FAMCARE, Family Satisfaction with Care; GDS, Geriatric Depression Scale; ADLs, activities of daily living; IADLs, Instrumental activities of daily living; LSNS-6, Lubben Social Network Scale; DT, single-item Distress Thermometer.

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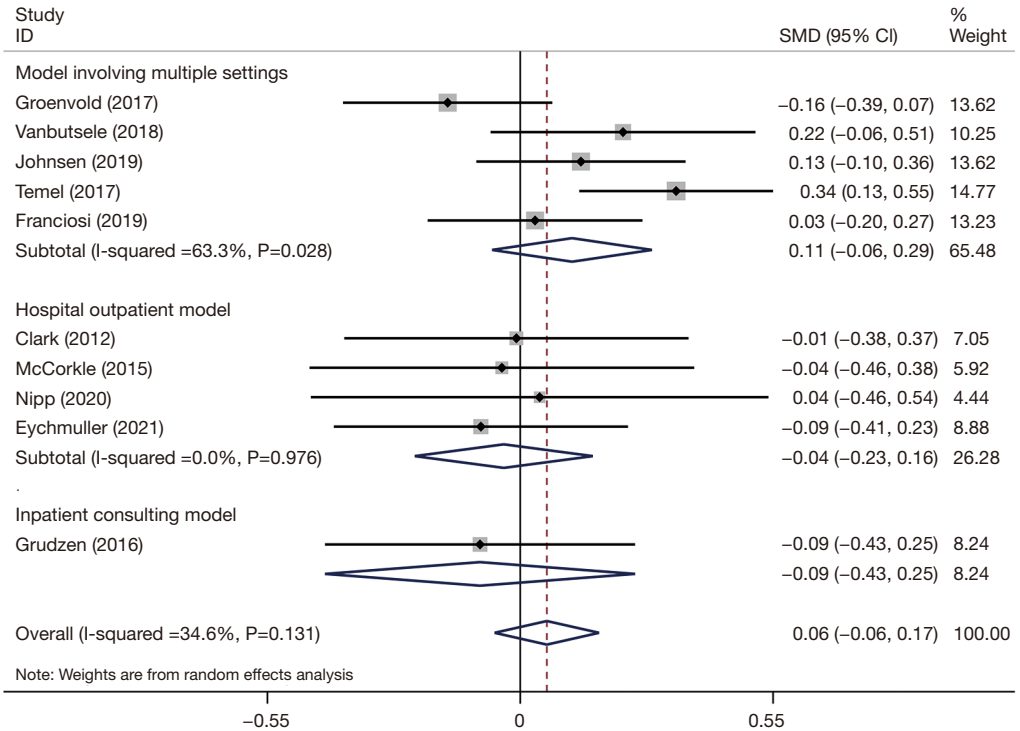

Figure 2 Meta-analysis showing effects of three different models of IPC on QoL in comparison to conventional treatment. Box size represents study weighting. Diamonds represent overall effect size and 95% CI. SMD, standardized mean difference; IPC, integrated palliative care; QoL, quality of life.

in the intervention group than in the control group (SMD =0.13, 95% CI: 0.02 to 0.24, P=0.016). At the 26–27 weeks follow-up, the QoL score change did not differ significantly between the groups (SMD =0.15, 95% CI: −0.06 to 0.25, P=0.153) (*Figure 3*).

Effects on depression symptoms

In the primary analysis, depression symptoms were lower in the IPC group than in the conventional care group, with marginal significance (SMD =−0.19, 95% CI: −0.39 to 0.00, P=0.053). Heterogeneity was moderate (I^2 = 57.1%, P=0.054). The patient-involved inpatient consulting model showed a significant improvement in depressive symptoms (SMD =−0.42, 95% CI: −0.64 to −0.19, P<0.001) with respect to the other two models (*Figure 4*). The results of the sensitivity analysis showed that the overall effect size did not change very much when removing studies consecutively, which indicated that our results were statistically reliable and robust. The sensitivity analysis is detailed in Figure S3. Subgroup analyses were performed according to follow-up duration (*Figure 5*). A significant improvement in depressive symptoms was identified at the 2-week follow-up (SMD =−0.30, 95% CI: −0.52 to −0.07, P=0.009); however, the outcomes of IPC group indicated that the depressive symptoms were statistically greater at the 3–4-week follow-up (SMD =0.22, 95% CI: 0.03 to 0.41, P=0.026) than in the usual care group. At the 8–12 weeks follow-up, the change in depressive symptoms did not differ significantly between the groups (SMD =−0.15, 95% CI: −0.38 to 0.08, P=0.209).

Effects on anxiety symptom

We compared the pooled effect size of IPC on anxiety symptoms to the control group in a random effects model. The overall analysis showed no significant difference between the two groups' anxiety symptoms (SMD =−0.12; 95% CI: −0.35 to 0.10; P=0.295) (*Figure 6*). Heterogeneity was moderate (I^2 = 52.1%, P=0.100). In the subgroup analyses of the three different models, a statistically significant difference was found for the inpatient consulting model versus conventional treatment (SMD =−0.31; 95% CI: −0.54 to −0.09; P=0.006) (*Figure 6*). According to the sensitivity analysis, the results remained stable and reliable (Figure S4).

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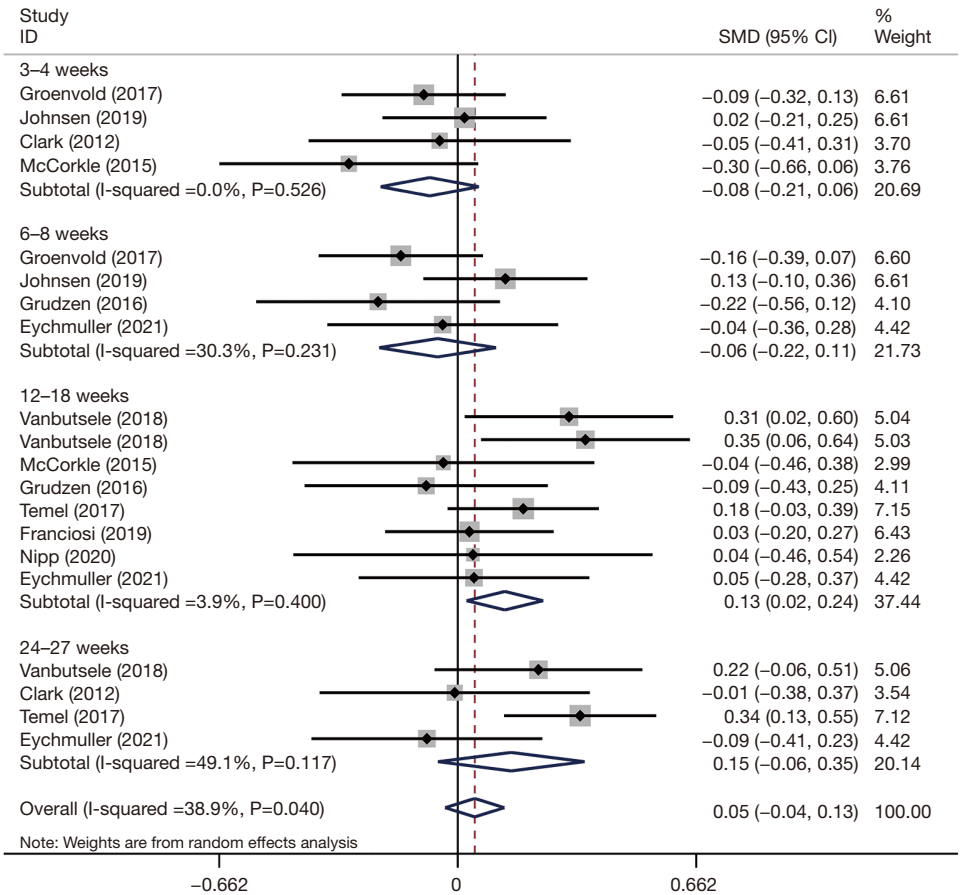

Figure 3 Long-term effect size of QoL (change from post-treatment to 3–4 weeks, 6–8 weeks, 12–18 weeks, 24–27 weeks follow-up). Box size represents study weighting. Diamond represents overall effect size and 95% CI. SMD, standardized mean difference; QoL, quality of life.

Furthermore, analyses were subgrouped by follow-up duration, and the IPC group had significantly fewer anxiety symptoms than the control group at the 2-week follow-up (SMD =−0.45, 95% CI: −0.68 to −0.23, P<0.001). At the 3–4 weeks and 8–12 weeks follow-ups, the change in anxiety symptoms did not differ significantly between the groups (SMD =0.18, 95% CI: −0.01 to 0.37, P=0.065; SMD =−0.04, 95% CI: −0.25 to 0.18, P=0.726) (*Figure 7*).

Effects on PTSD symptoms

Two studies reported the effect of IPC on PTSD symptoms. No significant heterogeneity was observed ($I^2 = 0\%$; P=0.640). The results showed that PTSD symptoms were significantly reduced in the IPC group compared with the conventional group (SMD =−0.46, 95% CI: −0.69 to −0.23, P<0.001) (*Figure 8*). Only two studies were included, and we did not perform subgroup analysis.

Risk of publication bias across studies

Egger's test was performed to evaluate the publication bias of the included studies. The funnel plot was symmetric for both QoL and psychological distress outcomes (Figure S5-S7), showing a lack of publication bias (P=0.309; P=0.852; P=0.962).

Discussion

In this meta-analysis, we assessed and synthesized clinical trial evidence of the effects of IPC on QoL and psychological distress outcomes in patients with advanced cancer. Our results suggested no significant difference between the three different models of IPC and conventional treatment on overall QoL. However, there was a long-lasting favorable effect of IPC on overall QoL throughout the follow-up time period of 12 to 18 weeks. There is an

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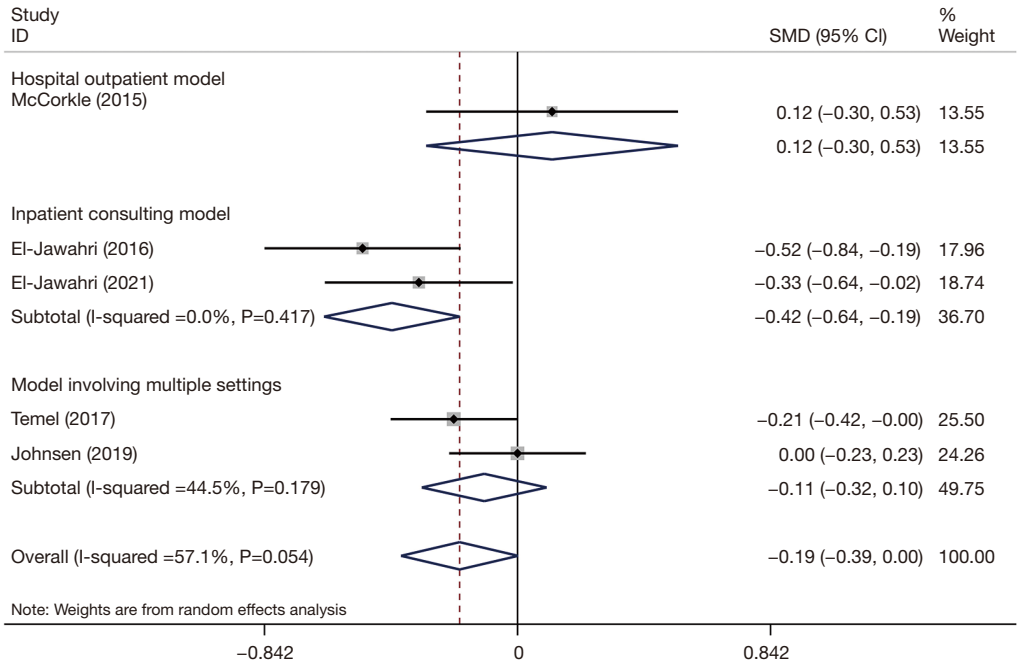

Figure 4 Meta-analysis showing effects of three different models of IPC on depression symptom in comparison to conventional treatment. Box size represents study weighting. Diamonds represent overall effect size and 95% CI. SMD, standardized mean difference; IPC, integrated palliative care.

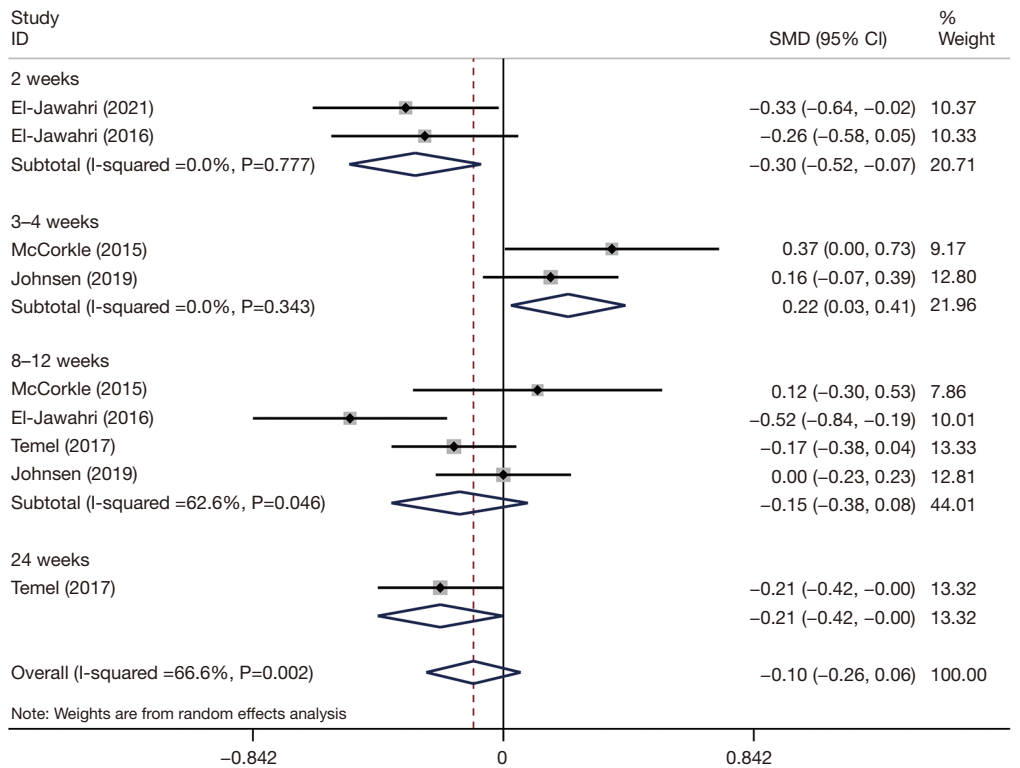

Figure 5 Long-term effect size of depression symptom (change from post-treatment to 2 weeks, 3–4 weeks, 8–12 weeks, 24 weeks follow-up). Box size represents study weighting. Diamond represents overall effect size and 95% CI. SMD, standardized mean difference.

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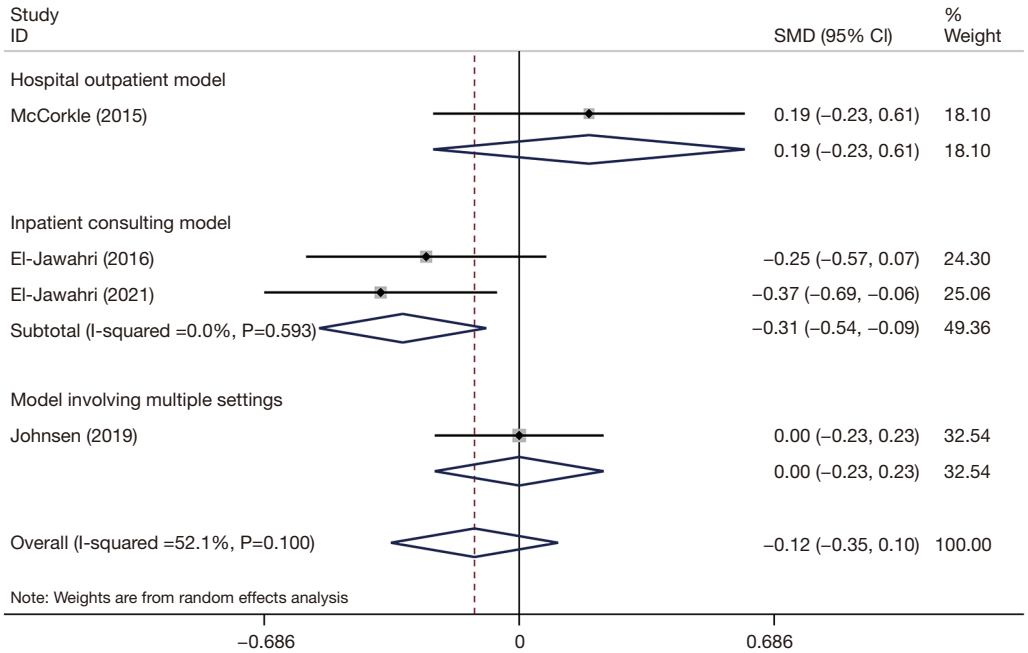

Figure 6 Meta-analysis showing effects of three different models of IPC on anxiety symptom in comparison to conventional treatment. Box size represents study weighting. Diamonds represent overall effect size and 95% CI. SMD, standardized mean difference; IPC, integrated palliative care.

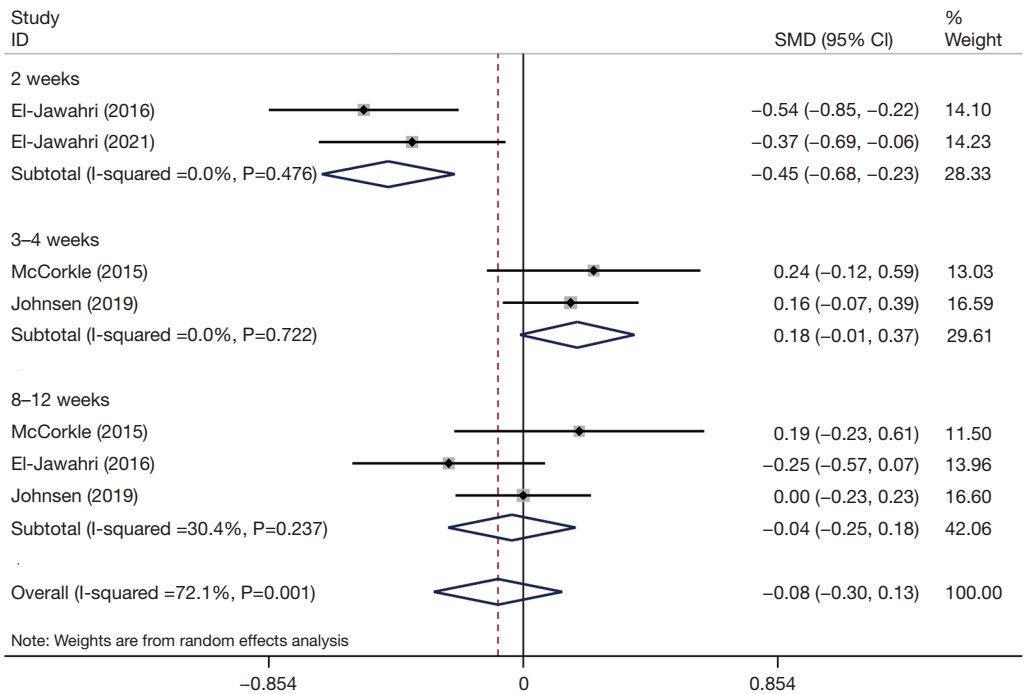

Figure 7 Long-term effect size of anxiety symptom (change from post-treatment to 2 weeks, 3–4 weeks, 8–12 weeks follow-up). Box size represents study weighting. Diamond represents overall effect size and 95% CI. SMD, standardized mean difference.

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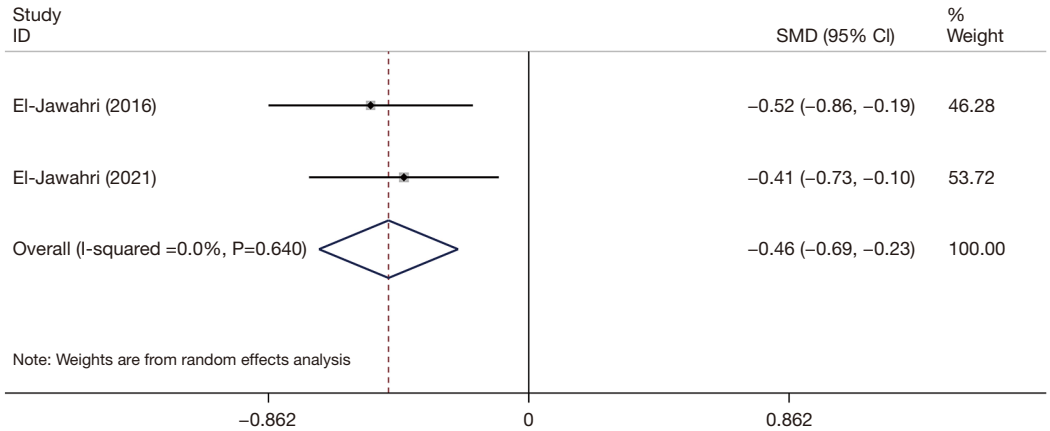

Figure 8 Meta-analysis showing effects of three different models of IPC on PTSD symptom in comparison to conventional treatment. Box size represents study weighting. Diamonds represent overall effect size and 95% CI. SMD, standardized mean difference; IPC, integrated palliative care; PTSD, posttraumatic stress disorder.

indication that the inpatient consulting model was more effective than the other models in reducing depression and anxiety symptoms. In the early follow-up period of approximately 2 weeks, IPC was shown to be significantly more effective on these symptoms. IPC was also effective in decreasing PTSD symptoms.

No significant differences in overall QoL were observed between IPC and conventional treatment. This finding was not consistent with previous meta-analysis results (32). However, we performed a more comprehensive systematic analysis and included the latest studies that the previous meta-analysis did not include. As is the case in most research settings of palliative care, the included trials differed largely in several aspects, such as the population studied, the outcomes chosen, the clinical setting, and the duration of the study. The true effect may be substantially different. Even when we separately examined the efficacy of the three models of IPC in our analysis, we did not find a significant difference in efficacy. Fulton *et al.* reported that there was no significant difference in patients' psychological distress between integrated outpatient palliative care treatment and conventional treatment (8). These results are consistent with our findings. Apart from that, we also found that the inpatient consulting model of IPC has a desirable effect on psychological distress. The mechanisms underlying these reductions in psychological distress in patients receiving inpatient palliative care are not completely clear. Palliative care may improve psychological conditions by providing patients with the skills to cope effectively with life-threatening illness (33). We speculate that it is plausible that inpatient palliative care is more effective for enhancing patients' adaptive coping strategies (34). Future work should examine whether patients' coping skills mediate the effect of different integration models of palliative care intervention on psychological distress in patients with advanced cancer.

Some evidence suggests that for the optimal therapeutic benefit of palliative care to be realized, continuity of intervention by a multidisciplinary team is needed for at least 3–4 months (35). This is confirmed by our results of long-term improvements (at the 12–18 weeks follow-up) in overall QoL. Our results regarding psychological distress showed that the IPC intervention for depression and anxiety symptoms was most effective at an early stage of approximately 2 weeks. Multidisciplinary palliative care teams frequently focus on coping strategies and managing expectations, which could potentially explain the psychological improvement (25). However, there was no difference in the long-term improvement of psychological distress between IPC and conventional care in patients with advanced cancer. Given the high mortality and disease burden among this population, possible confounders (e.g., health care utilization and end-of-life outcomes) should be comprehensively considered in future work.

This meta-analysis provides high-quality evidence that IPC are potentially effective in improving QoL and relieving psychological distress for advanced cancer patients. Compared with previous meta-analyses, this meta-analysis explored these outcomes according to various types of IPC but also according to the follow-up time/period. Our meta-analysis was conducted as a Cochrane review following

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the instructions from the Cochrane Handbook and the PRISMA guidelines.

Study limitations

There are several limitations to the present meta-analysis that should be addressed prior to its application in clinical practice. Between-study heterogeneity persisted in some of the subgroups, suggesting the presence of other potentially confounding factors, resulting from differences in the intervention models, length of intervention, diversity in sample sizes, patient ages, cancer types, and other factors. In addition, it was difficult to include more patients with different types of cancer because retrospective cohorts and observational studies did not meet our inclusion criteria. RCTs provide high-level evidences but are sometimes not feasible due to ethical issues, substantial costs, and inadequate duration of follow-up. Thus, a more comprehensive meta-analysis is needed with more cases. Furthermore, we did not have access to sufficient data to determine whether IPC increased all dimensions of the patients' QoL. Notwithstanding these limitations, the current study provides important evidence suggesting the efficacy of IPC for patients with advanced cancer in improving overall QoL and reducing psychological distress.

Clinical implications

This meta-analysis has implications for both research and clinical practice. It provides a comprehensive overview of the available randomized evidence on the effectiveness of IPC treatment for emotional distress and QoL in patients with advanced cancer. We had a specific focus on various integration models and the long-term efficacy of IPC. Our results may imply that the inpatient consultation model is more favorable for reducing depression and anxiety symptoms, especially in the early period of approximately 2 weeks. This may assist in guiding clinicians in making early treatment decisions in clinical practice. However, our analyses are based on reports of depressive and anxiety symptoms, not diagnoses of disorders. It will be important in future research to determine whether IPC decreases the risk for mood or anxiety disorders in patients with advanced cancer. Furthermore, future studies should use a consensus-based measure of QoL that assesses as many domains as possible (physical, psychosocial, spiritual). Finally, our results highlight the need for further research assessing long-term real-world data on the psychological profiles of patients receiving different versions of IPC as well as the effects on QoL. These observations should guide future research and clinical practice.

Conclusions

Our results suggest that IPC can effectively improve the QoL and alleviate early psychological distress of patients with advanced cancer. There is an indication that the inpatient consulting model was more effective than other models in reducing depression and anxiety symptoms. These results were based on randomized clinical trial studies and require further verification.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-162/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-162/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

1. Latest global cancer data: Cancer burden rises to 19.3 million new cases and 10.0 million cancer deaths in 2020. Available online: https://www.iarc.who.int/news-events/latest-global-cancer-data-cancer-burden-rises-to-19-3-million-new-cases-and-10-0-million-cancer-deaths-in-2020/
2. Skov Benthien K, Adsersen M, Petersen MA, et al. Is specialized palliative cancer care associated with use of antineoplastic treatment at the end of life? A population-based cohort study. Palliat Med 2018;32:1509-17.
3. Bakitas MA, Tosteson TD, Li Z, et al. Early Versus Delayed Initiation of Concurrent Palliative Oncology Care: Patient Outcomes in the ENABLE III Randomized Controlled Trial. J Clin Oncol 2015;33:1438-45.
4. Heywood R, McCarthy AL, Skinner TL. Efficacy of Exercise Interventions in Patients With Advanced Cancer: A Systematic Review. Arch Phys Med Rehabil 2018;99:2595-620.
5. Shin J, Temel J. Integrating palliative care: when and how? Curr Opin Pulm Med 2013;19:344-9.
6. Greer JA, Jackson VA, Meier DE, et al. Early integration of palliative care services with standard oncology care for patients with advanced cancer. CA Cancer J Clin 2013;63:349-63.
7. Ferrell BR, Temel JS, Temin S, et al. Integration of Palliative Care Into Standard Oncology Care: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2017;35:96-112.
8. Fulton JJ, LeBlanc TW, Cutson TM, et al. Integrated outpatient palliative care for patients with advanced cancer: A systematic review and meta-analysis. Palliat Med 2019;33:123-34.
9. Oluyase AO, Higginson IJ, Yi D, et al. Health Services and Delivery Research, in Hospital-based specialist palliative care compared with usual care for adults with advanced illness and their caregivers: a systematic review. Southampton (UK): NIHR Journals Library, 2021.
10. Hoerger M, Wayser GR, Schwing G, et al. Impact of Interdisciplinary Outpatient Specialty Palliative Care on Survival and Quality of Life in Adults With Advanced Cancer: A Meta-Analysis of Randomized Controlled Trials. Ann Behav Med 2019;53:674-85.
11. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264-9, W64.
12. Lynn J, Adamson DM. Living Well at the End of Life: Adapting Health Care to Serious Chronic Illness in Old Age. 2003. Available online: https://apps.dtic.mil/sti/pdfs/ADA416211.pdf
13. Higgins JP. Cochrane handbook for systematic reviews of interventions version 5.0. 1. The Cochrane Collaboration. Available online: http://www.cochrane-handbook.org
14. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
15. Clark MM, Rummans TA, Atherton PJ, et al. Randomized controlled trial of maintaining quality of life during radiotherapy for advanced cancer. Cancer 2013;119:880-7.
16. McCorkle R, Jeon S, Ercolano E, et al. An Advanced Practice Nurse Coordinated Multidisciplinary Intervention for Patients with Late-Stage Cancer: A Cluster Randomized Trial. J Palliat Med 2015;18:962-9.
17. Grudzen CR, Richardson LD, Johnson PN, et al. Emergency Department-Initiated Palliative Care in Advanced Cancer: A Randomized Clinical Trial. JAMA Oncol 2016;2:591-8.
18. Groenvold M, Petersen MA, Damkier A, et al. Randomised clinical trial of early specialist palliative care plus standard care versus standard care alone in patients with advanced cancer: The Danish Palliative Care Trial. Palliat Med 2017;31:814-24.
19. Temel JS, Greer JA, El-Jawahri A, et al. Effects of Early Integrated Palliative Care in Patients With Lung and GI Cancer: A Randomized Clinical Trial. J Clin Oncol 2017;35:834-41.
20. Vanbutsele G, Pardon K, Van Belle S, et al. Effect of early and systematic integration of palliative care in patients with advanced cancer: a randomised controlled trial. Lancet Oncol 2018;19:394-404.
21. Franciosi V, Maglietta G, Degli Esposti C, et al. Early palliative care and quality of life of advanced cancer patients-a multicenter randomized clinical trial. Ann Palliat Med 2019;8:381-9.
22. Johnsen AT, Petersen MA, Sjøgren P, et al. Exploratory analyses of the Danish Palliative Care Trial (DanPaCT): a randomized trial of early specialized palliative care plus standard care versus standard care in advanced cancer patients. Support Care Cancer 2020;28:2145-55.
23. Eychmüller S, Zwahlen S, Fliedner MC, et al. Single early palliative care intervention added to usual oncology care for patients with advanced cancer: A randomized controlled trial (SENS Trial). Palliat Med 2021;35:1108-17.
24. Nipp RD, Temel B, Fuh CX, et al. Pilot Randomized

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Trial of a Transdisciplinary Geriatric and Palliative Care Intervention for Older Adults With Cancer. J Natl Compr Canc Netw 2020;18:591-8.
25. El-Jawahri A, LeBlanc T, VanDusen H, et al. Effect of Inpatient Palliative Care on Quality of Life 2 Weeks After Hematopoietic Stem Cell Transplantation: A Randomized Clinical Trial. JAMA 2016;316:2094-103.
26. El-Jawahri A, LeBlanc TW, Kavanaugh A, et al. Effectiveness of Integrated Palliative and Oncology Care for Patients With Acute Myeloid Leukemia: A Randomized Clinical Trial. JAMA Oncol 2021;7:238-45.
27. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365-76.
28. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol 1993;11:570-9.
29. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-70.
30. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16:606-13.
31. Smith MY, Redd W, DuHamel K, et al. Validation of the PTSD Checklist-Civilian Version in survivors of bone marrow transplantation. J Trauma Stress 1999;12:485-99.
32. Gaertner J, Siemens W, Meerpohl JJ, et al. Effect of specialist palliative care services on quality of life in adults with advanced incurable illness in hospital, hospice, or community settings: systematic review and meta-analysis. BMJ 2017;357:j2925.
33. Greer JA, Jacobs JM, El-Jawahri A, et al. Role of Patient Coping Strategies in Understanding the Effects of Early Palliative Care on Quality of Life and Mood. J Clin Oncol 2018;36:53-60.
34. Amano K, Hopkinson J, Baracos V. Psychological symptoms of illness and emotional distress in advanced cancer cachexia. Curr Opin Clin Nutr Metab Care 2021. doi: 10.1097/MCO.0000000000000815. [Epub ahead of print].
35. Davis MP, Temel JS, Balboni T, et al. A review of the trials which examine early integration of outpatient and home palliative care for patients with serious illnesses. Ann Palliat Med 2015;4:99-121.

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Appendix 1

Search strategy PubMed

Set	Terms
#1	"Neoplasms"[Mesh] OR "Neoplasia"[tiab] OR "Neoplasias"[tiab] OR "Neoplasm"[tiab] OR "Tumors"[tiab] OR "Tumor"[tiab] OR "Cancer"[tiab] OR "Cancers"[tiab] OR "Malignancy"[tiab] OR "Malignancies"[tiab] OR "Malignant Neoplasms"[tiab] OR "Malignant Neoplasm"[tiab] OR "Neoplasm, Malignant"[tiab] OR "Neoplasms, Malignant"[tiab]
#2	"Palliative Care"[Mesh] OR "Hospice and Palliative Care Nursing"[Mesh] OR "Palliative Medicine"[Mesh] OR "Care, Palliative"[tiab] OR "Palliative Treatment"[tiab] OR "Palliative Treatments"[tiab] OR "Treatment, Palliative"[tiab] OR "Treatments, Palliative"[tiab] OR "Therapy, Palliative"[tiab] OR "Palliative Therapy"[tiab] OR "Palliative Supportive Care"[tiab] OR "Supportive Care, Palliative"[tiab] OR "Palliative Surgery"[tiab] OR "Surgery, Palliative"[tiab] OR "Palliative Nursing"[tiab] OR "Palliative Care Nursing"[tiab] OR "Hospice Nursing"[tiab] OR "Hospice Nursings"[tiab] OR "Nursing, Hospice"[tiab] OR "Nursings, Hospice"[tiab] OR "Palliative Care Medicine"[tiab] OR "Medicine, Palliative Care"[tiab] OR "Medicine, Palliative"[tiab]
#3	"Psychological Distress"[Mesh] OR "Anxiety"[Mesh] OR "Depression"[Mesh] OR "Quality of Life"[Mesh] OR "Distress, Psychological"[tiab] OR "Emotional Distress"[tiab] OR "Distress, Emotional"[tiab] OR "Emotional Stress"[tiab] OR "Stress, Emotional"[tiab] OR "Angst"[tiab] OR "Nervousness"[tiab] OR "Hypervigilance"[tiab] OR "Anxiousness"[tiab] OR "Social Anxiety"[tiab] OR "Anxieties, Social"[tiab] OR "Anxiety, Social"[tiab] OR "Social Anxieties"[tiab] OR "Depressions"[tiab] OR "Depressive Symptoms"[tiab] OR "Depressive Symptom"[tiab] OR "Symptom, Depressive"[tiab] OR "Symptoms, Depressive"[tiab] OR "Emotional Depression"[tiab] OR "Depression, Emotional"[tiab] OR "Depressions, Emotional"[tiab] OR "Emotional Depressions"[tiab] OR "Life Quality"[tiab] OR "Health-Related Quality Of Life"[tiab] OR "Health Related Quality Of Life"[tiab] OR "HRQOL"[tiab]
#4	(("randomized controlled trial"[pt] OR "Controlled Clinical Trial"[pt] OR "randomized"[tiab] OR "randomised"[tiab] OR "randomization"[tiab] OR "randomisation"[tiab] OR "placebo"[tiab] OR "randomly"[tiab] OR "trial"[tiab] OR "groups"[tiab] OR "Comparative Study"[pt] OR "Controlled Clinical Trial"[pt] OR "Nonrandom"[tiab] OR "Nonrandom"[tiab] OR "nonrandomized"[tiab] OR "non-randomized"[tiab] OR "nonrandomized"[tiab] OR "non-randomised"[tiab] OR "quasi experiment*"[tiab] OR "quasiexperiment*"[tiab] OR "quasirandom*"[tiab] OR "quasi random*"[tiab] OR "quasi control*"[tiab] OR "quasicontrol*"[tiab] OR ("controlled"[tiab] AND ("trial"[tiab] OR "study"[tiab]))) NOT ("animals"[Mesh] NOT "humans"[Mesh])) NOT ("Editorial"[pt] OR "Letter"[pt] OR "case reports"[pt] OR "Comment"[pt])
#5	#1 AND #2 AND #3 AND #4

Search strategy EMBASE

('advanced cancer'/exp OR 'terminal cancer'/exp OR 'malignant neoplasm'/exp OR 'cancer' OR 'cancers' OR 'malignant neoplasia' OR 'malignant neoplasm' OR 'malignant neoplastic disease' OR 'malignant tumor' OR 'malignant tumour' OR 'neoplasia, malignant' OR 'tumor, malignant' OR 'tumour, malignant') AND ('palliative therapy'/exp OR 'palliation' OR 'palliative care' OR 'palliative consultation' OR 'palliative medicine' OR 'palliative radiotherapy' OR 'palliative surgery' OR 'palliative therapy' OR 'palliative treatment' OR 'symptomatic treatment') AND ('mental disease assessment'/exp OR 'mental disease assessment' OR 'psychiatric disorder assessment') AND ('randomized controlled trial'/exp OR 'controlled trial, randomized' OR 'randomised controlled study' OR 'randomised controlled trial' OR 'randomized controlled study' OR 'randomized controlled trial' OR 'trial, randomized controlled')

Search strategy Cochrane Library

#1 MeSH descriptor: [Neoplasms] explode all trees 83,592
#2 (Neoplasia):ti,ab,kw (Word variations have been searched) 3,038
#3 (Tumor):ti,ab,kw (Word variations have been searched) 76,773
#4 (cancer):ti,ab,kw (Word variations have been searched) 172,435
#5 (Malignancy):ti,ab,kw (Word variations have been searched) 27,817
#6 #1 OR #2 OR #3 OR #4 OR #5 231,645
#7 (Palliative Care):ti,ab,kw (Word variations have been searched) 4,959

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#8 (Psychological Distress):ti,ab,kw (Word variations have been searched) 8,562
#9 (Depression):ti,ab,kw (Word variations have been searched) 91,972
#10 (Anxiety):ti,ab,kw (Word variations have been searched) 56,170
#11 (Quality of Life):ti,ab,kw (Word variations have been searched) 127,645
#12 #8 OR #9 OR #10 OR #11 228,516
#13 #6 AND #7 AND #12 1,711

Search strategy psycINFO

The qualified condition is RCT
((terminal cancer) OR (advanced cancer) OR Malignancy OR Tumor OR Neoplasms) AND ((Palliative Care) OR (Hospice and Palliative Care Nursing) OR (Palliative Medicine) OR (Palliative Treatment)) AND ((Psychological Distress) OR (Anxiety) OR (Depression) OR (Quality of Life) OR (Emotional Distress))

Search strategy CINAHL

Qualifications - English; Research papers; Do not include the Pre - CINAHL; Exclude MEDLINE records; Humans; Age group: All Adult Search mode - Boolean logic/phrase
((terminal cancer) OR (advanced cancer) OR Malignancy OR Tumor OR Neoplasms) AND ((Palliative Care) OR (Hospice and Palliative Care Nursing) OR (Palliative Medicine) OR (Palliative Treatment)) AND ((Psychological Distress) OR (Anxiety) OR (Depression) OR (Quality of Life) OR (Emotional Distress))

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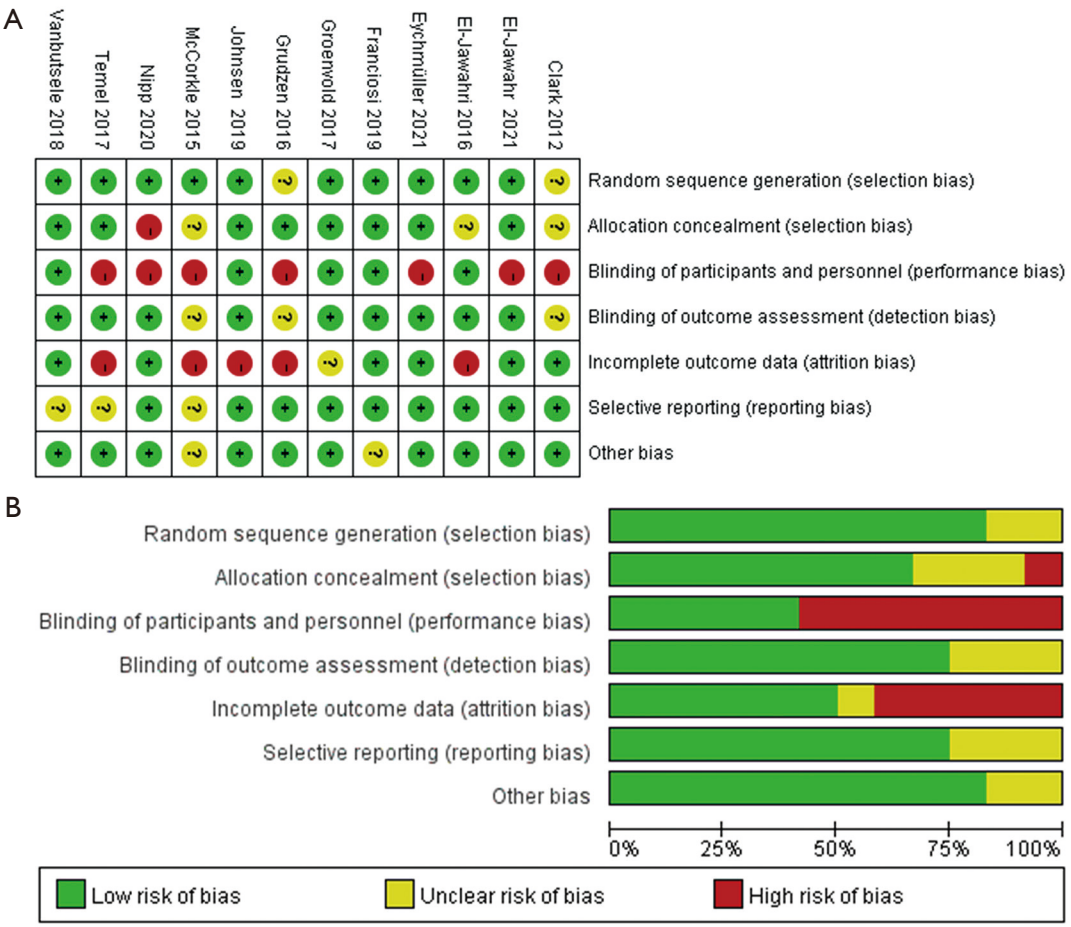

Figure S1 Quality assessment of RCTs. (A) Risk of bias summary: review authors' judgments about each risk of bias item for each included study. (B) Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

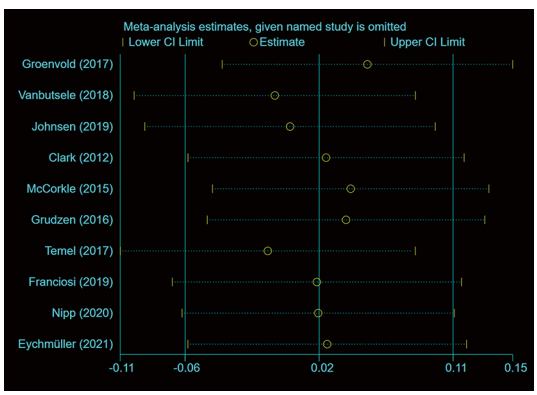

Figure S2 The forest plot of the sensitivity analysis of IPC on overall QoL.

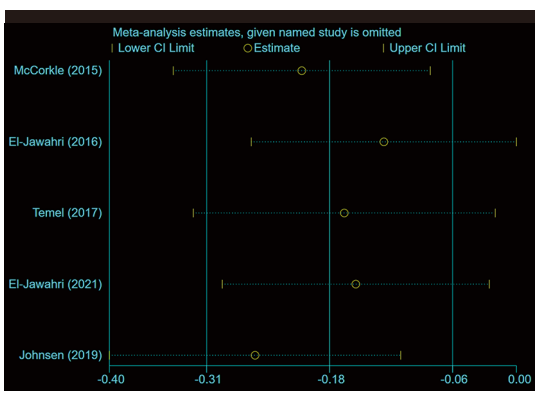

Figure S3 The forest plot of the sensitivity analysis of IPC on depression symptom.

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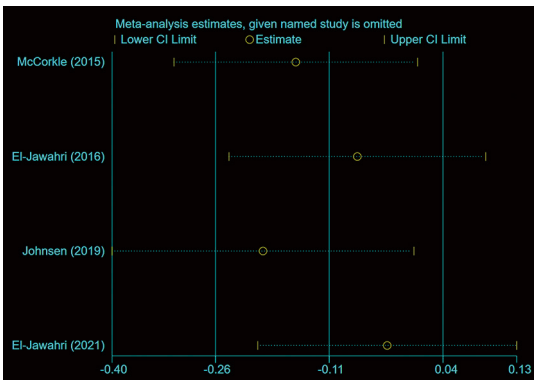

Figure S4 The forest plot of the sensitivity analysis of IPC on anxiety symptom.

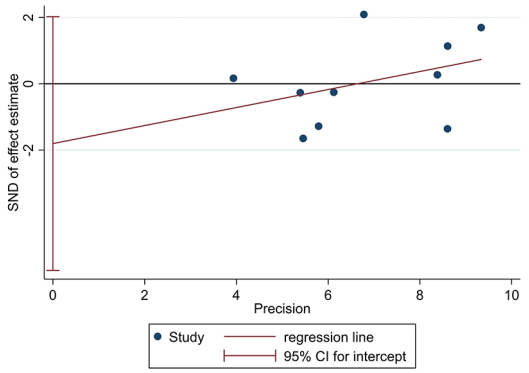

Figure S5 Funnel plot for publication bias on overall QoL.

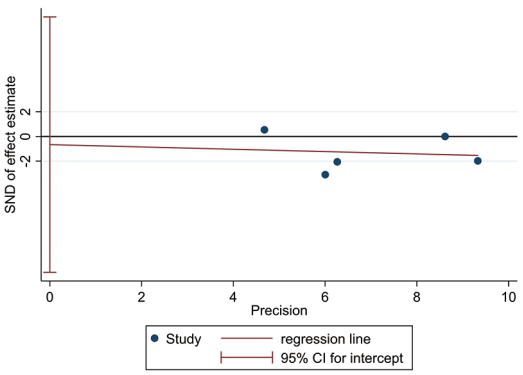

Figure S6 Funnel plot for publication bias on depression symptom.

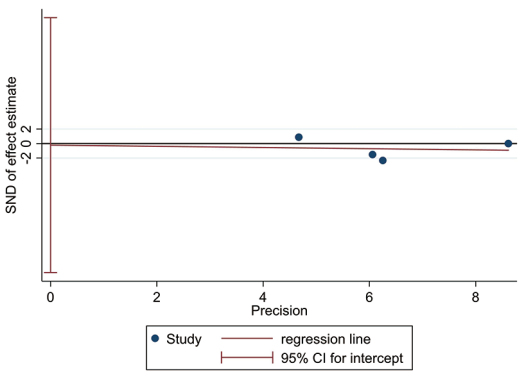

Figure S7 Funnel plot for publication bias on anxiety symptom.

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